



REMARKS

1-Requirement for Restriction

The examiner required restriction to one of several groups of targets recited in the claims under 35 USC 1.121. The applicant has selected the receptor targets, as described above.

2- Amendment

THE CLAIMS

Claims 1-91 are pending in this application, and no claims have been amended. Consideration and allowance of these claims is requested.

THE SPECIFICATION

The applicant submitted with the Amendment of September 28, 2001, marked-up and clean copies of the amended specification pages. Further copies are enclosed herewith for the examiner's convenience. The amendments to the specification are fully supported by the specification, as filed and by the original claims. No objectionable new matter is believed to have been introduced by this amendment.

THE FEE

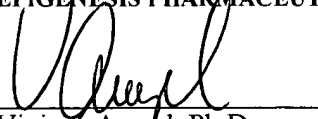
The Assistant Commissioner, however, is hereby authorized to charge to PTO Account No. 50-1728, the amount of \$200.- for an extension fee of two months, which is herewith being requested. In view of the above amendments and remarks, this application is believed to be in condition for examination and allowance. Early notice to that effect is hereby solicited.

January 4, 2002

Date

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I hereby certify that this correspondence is being deposited at the United States Postal Service, First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington D C 20231, on January 4, 2002, by Rashida Haji.

SIGNATURE



VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification

Section beginning from page 296, line 56, to page 298, line 60, has been amended as follows (from next page):



GGATATAGGT TTCCAATTAA GTACATGGTC AAGTATTAAC AGCACAAGTG GTAGGTTAAC ATTAGAATAG
 GAATTGGTGT TGGGGGGGGG GTTTGCAAGA ATATTTTATT TTAATTTTTT GGATGAAATT TTTATCTATT
 ATATATTAAA CATTCTTGCT GCTGCGCTGC AAAGCCATAG CAGATTGAG GCGCTGTTGA GGACTGAATT
 ACTCTCCAAG TTGAGAGATG TCTTTGGGTT AAATTAAGAG CCCTACCTAA AACTGAGGTG GGGATGGGGA
 5 GAGCCTTTGC CTCCACCATT CCCACCCACC CTCCCCTTAA ACCCTCTGCC TTTGAAAGTA GATCATGTTT
 ACTGCAATGC TGGACACTAC AGGTATCTGT CCCTGGGCCA GCAGGGACCT CTGAAGCCTT CTTTGTGGCC
 TTTTTTTTTT TTCATCCTGT GGTTTTCTA ATGGACTTTC AGGAAATTTG TAATCTCATA ACTTTCCAAG
 CTCCACCCTT TCCTAAATCT TAAGAACTTT AATTGACAGT TTCAATTGAA GGTGCTGTTT GTAGACTTAA
 CACCCAGTGA AAGCCCAGCC ATCATGACAA ATCCTTGAAT GTTCTCTTAA GAAAATGATG CTGGTCATCG
 CAGCTTCAGC ATCTCCTGTT TTTTGATGCT TGGCTCCCTC TGCTGATCTC AGTTTCCTGG CTTTTCCTCC
 CTCAGCCCCT TCTCACCCTT TTGCTGTCTT GTGTAGTGAT TTGGTGAGAA ATCGTTGCTG CACCCTTCCC
 CCAGCACCAT TATGAGTCT CAAGTTTAT TATTGCAATA AAAGTGCTTT ATGCCCGAAT TC-3' (FRAG.NO:_)

(SEQ. ID NO:2497)

5' GCCGCCGCCA TGGGAGTGCA GGTGGAAACC ATCTCCCCAG GAGACGGGCG CACCTTCCCC AAGCGCGGCC
 15 AGACCTGCGT GGTGCACTAC ACCGGGATGC TTGAAGATGG AAAGAAATTT GATTCTCCC GGGACAGAAA
 CAAGCCCTTT AAGTTTATGC TAGGCAAGCA GGAGGTGATC CGAGGCTGGG AAGAAGGGGT TGCCAGATG
 AGTGTGGGTC AGAGAGCCAA ACTGACTATA TCTCCAGATT ATGCCTATGG TGCCACTGGG CACCCAGGCA
 TCATCCACC ACATGCCACT CTCGTCTTCG ATGTGGAGCT TCTAAACTG GAATGACAGG AATGGCCTCC
 20 TCCCTTAGCT CCCTGTCTT GGATCTGCCR TGGAGGGATC TGGTGCCTCC AGACATGTGC ACATGARTCC
 ATATGGAGCT TTTCTGATG TTCCACTCCA CTTTGTATAG ACATCTGCCC TGACTGAATG TGTCTGTCA
 CTCAGCTTTG CTTCCGACAC CTCTGTTTCC TCTTCCCTT TCTCCTCGTA TGTGTGTTA CCTAAACTAT
 ATGCCATAAA CCTCAAGTTA TTCA-3' (FRAG. NO:_) (SEQ. ID NO:2498)

wherein B is adenosine, or, more preferably, replaces adenosine and is an "equivame\\lent" or a "universal"
 base, and adenosine A_{2a} receptor agonist or only minimally antagonist, an adenosine A_{2b} receptor antagonist,
 25 an adenosine A₃ receptor antagonist, or an adenosine A₁ receptor antagonist. Similarly, adenosine (A) may
 always be replaced by an "alternative", "equivalent" and/or "universal" base having a small fraction,
 preferably less than 0.3 of the activity of adenosine at the adenosine receptor(s), as described above.

In one preferred embodiment, the links between neighboring mononucleotides are phosphodiester
 links. In another preferred, at least one mononucleotide phosphodiester residue of the anti-sense
 30 oligonucleotide(s) is substituted by a methylphosphonate, phosphotriester, phosphorothioate,
 phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate,
 sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, 2'-O-methyl,
 methylene(methylimino), methyleneoxy (methylimino), phosphoramidate residues, and combinations thereof.
 The oligos having one or more phosphodiester residues substituted by one or more of the other residues are
 35 generally longer lasting, given that these residues are more resistant to hydrolysis than the phosphodiester
 residue. In some cases up to about 10%, about 30%, about 50%, about 75%, and even all phosphodiester
 residues may be substituted (100%). Typically, the multiple target anti-sense oligonucleotide (oligo) of the
 invention comprises at least about 7 mononucleotides, in some instances up to 60 and more mononucleotides,
 preferably about 10 to about 36, and more preferably about 12 to about 21 mononucleotides. However, other
 40 lengths are also suitable depending on the length of the target macromolecule. Examples of the MTA oligos of
 the invention are provided in Table 3 below, which includes ninety-four sequences (SEQ ID NOS.: 2316
 through 2410).

Table 3: MTA Oligos, Location Targeted & Target

MTA Oligo	SEQ. ID No.	Location	Compound Targeted	Target
<u>HUMNFKBP65A AS</u>				
CCC GGC CCC GCC TCG TGC C	3019	5' =1	EPI 2192	
CGT CCB TGC CGC GGG CCC	3020	5' =28 (AUG)	EPI 2193	
GCC CCG CTG CTT GGG CTG CTC TGC CGG G	3021	5' =65	EPI 2194	
50 TCT GTG CTC CTC TCG CCT GGG	3022	5' =137	EPI 2195	
TGG TGG GGT GGG TCT TGG TGG	3023	5' =159	EPI 2196	
CTG TCC CTG GTC CTG TG	3024	5' =196	EPI 2197	
GGT CCC GCT TCT TC	3025	5' =362	EPI 2198	
GGG GTT GTT GTT GGT CTG G	3026	5' =401	EPI 2199	
55 TGT CCT CTT TCT GC	3027 [3026]	5' =656	EPI 2200	
GCC TCG GGC CTC CC	3028 [3027]	5' =697	EPI 2201	
GGC TGG GGT CTG CGT	3029 [3028]	5' =769	EPI 2202	

	GGC CGG GGG TCG GTG GGT CCG CTG	<u>3030</u> [3029]	5'=953	EPI 2203	
	GGG CTG GGG TGC TGG CTT GGG G	<u>3031</u> [3030]	5'=1022	EPI 2204	
	GGG GCT GGG GCC TGG GCC	<u>3032</u> [3031]	5'=1208	EPI 2205	
	GCC TGG GTG GGC TTG GGG GC	<u>3033</u> [3032]	5'=1272	EPI 2206	
5	GCT GGG TCT GTG CTG TTG CC	<u>3034</u> [3033]	5'=1362	EPI 2207	
	GTT GTG TGG GGG GCC	<u>3035</u> [3034]	5'= 1451	EPI 2208	
	GCT GGG TCG GGG GGC CTC TGG GCT GTC	<u>3036</u> [3035]	5'=1511	EPI 2209	
	GCC CCG GGG CCC CC	<u>3037</u> [3036]	5'=1550	EPI 2210	
	TGG CTC CCC CCT CC	<u>3038</u> [3037]	5'=1772	EPI 2211	
10	GCT CCC CCC TTT CC	<u>3039</u> [3038]	5'=1863	EPI 2212	
	CGG ACG AAG ACA GAG A	<u>3040</u> [3039]	5'=1979	EPI 2213	
	GGC TTT GTG GGC TC	<u>3041</u> [3040]	5'=2011	EPI 2214	
	GCC TGC TCT CCC CC	<u>3042</u> [3041]	5'=2312	EPI 2215	
	CCC GGC CCC GCC BCG BBC C	<u>3043</u> [3042]	intron	EPI 2192-01A	HSU50136C4Synth
15	CCC GGC CCC GCC BCG	<u>3044</u> [3043]	intron	EPI 2192-01B	
	CCC GGC CCC GCC BCG BBC C	<u>3045</u> [3044]	5'untr	EPI 2192-02A	HUMLIPOX5LO
	CCC GGC CCC GCC BCG	<u>3046</u> [3045]	5'untr	EPI 2192-02B	
	CCC GBC CCC GCC TCB BG	<u>3047</u> [3046]	trans	EPI 2192-03A	HSNFKBS Subunit
	CCC GBC CCC GCC TC	<u>3048</u> [3047]	trans	EPI 2192-03B	
20	CCG GCC CCG CCT C	<u>3049</u> [3048]	5'untr	EPI 2192-04	TGFβR1
	CCC GBB CCC GCB TBG TGC C	<u>3050</u> [3049]	5'trans	EPI 2192-05A	HSU58198I1 enhan
	CCC GCB TBG TGC C	<u>3051</u> [3050]	5'untr	EPI 2192-05B	
	CCC GGB CCC BCC BBG TGC C	<u>3052</u> [3051]	3'trans	EPI 2192-06	HSVECAD
	CBG BBC CCG CCT CGT GCC	<u>3053</u> [3052]	intron	EPI 2192-07A	NFKB2
25	C CCG CCT CGT GCC	<u>3054</u> [3053]	intron	EPI 2192-07B	NFKB2
	CCG GCB CCG CCT CBT GCC	<u>3055</u> [3054]	5'trans	EPI 2192-08	Carboxypep
	CCG GCC CCG CCB CBT GCC	<u>3056</u> [3055]	3'trans	EPI 2192-09	HumADRA2Cα2AdrKid
	CCC GBC CCC GBC TCG	<u>3057</u> [3056]	5'untrs	EPI 2192-10	HUMFK506B
	CCC GGC CBC GBC TCG	<u>3058</u> [3057]	5'untrs	EPI 2192-11	HSNBARKS1βAdrKin
30	CCC GGC CCB GCC TBG	<u>3059</u> [3058]	5'UTR	EPI 2192-12	HSNFXN1 (NFKB1)
	CCC GGC BCB GBC TCG TBC C	<u>3060</u> [3059]	3'UTR	EPI 2192-13	HSILF (transcrp. Factor ILF)
	CCC GGC CCC GCC BCG	<u>3061</u> [3060]		EPI-2192-14	NFKB/C4Syn/5-LO/ TGFBrec1 MTA
35	CCC GGC CCC GCC BCG	<u>3062</u> [3061]		EPI-2192-15	NFKB/C4Syn/5-LOMTA
	TCC BTG CCG CGG GC	<u>3063</u> [3062]	3' trans	EPI-2193-01	METOncoGene
	TCC BTG CCB CGG GCC	<u>3064</u> [3063]	3' trans	EPI-2193-02	HSFGR2 (IG)
	TCC BTG CCB CGG GCC	<u>3065</u> [3064]	mid cod	EPI-2193-03	5-LO
	TCC BTG CCB CBG GCC	<u>3066</u> [3065]	mid cod	EPI-2193-04	HUMTK14
40	GTC CBT GBC GCG G	<u>3067</u> [3066]	3'trans	EPI-2193-05	HUMTNFR
	TC CBT GBC GCG GG	<u>3068</u> [3067]	AUG		Probl.HUMPTCH cardiacK+channel
	TCT GBG CTC CTC TBB CCT GGG	<u>3069</u> [3068]	intr	EPI-2195-01	humCSPAcytotox. Ser. Protease
45	CTG TGC BCC TBB CBC CTG GG	<u>3070</u> [3069]	intr	EPI-2195-02	HSINOSX08induc.NOS
	TGT GBT CCB CTB GBC TGG G	<u>3071</u> [3070]		EPI-2195-03	HUMACHRM2musc.m2 acetylch.rec.
	TCT GTB CTC BBC TCB CCT G	<u>3072</u> [3071]		EPI-2195-04	s86371s1 Neurokinin3Recept
50	TGC TCC TCB CBB CTG GG	<u>3073</u> [3072]	EPI-2195-05	HUMMIP1 Amacro	
	inflam.factor				

Table 3: MTA Oligos, Location Targeted & Target (Cont'd)

MTA Oligo	SEQ. ID No.	Location	Compound Targeted	Target
5 CTC CTC TBG CCT GG	<u>3074</u> [3073]		EPI-2195-06	HSNBARKS4
GTG CTC CBB TCB BCT GGG	<u>3075</u> [3074]		EPI-2195-07	β -Adr Rec Kinase
GTG CBC CBB TCB CCT GGG	<u>3076</u> [3075]		EPI-2195-08	HSTNFR2SO6TNF R2
				humfkbk fk506 binding prot.
10 TCT GTG CBC CTC TBG BCT	<u>3077</u> [3076]	exon	EPI-2195-09	HSNBARKS1 β -Adr. Recept. Kinase
CTG TBB TCC TBB CBC CTG G	<u>3078</u> [3077]	intron	EPI-2195-10	HUMIL8
TGT GCT BBT CBC BCB TGG G	<u>3079</u> [3078]		EPI-2195-11	HSU50157 PDE4
GTG CBC CBC TCB CCT G	<u>3080</u> [3079]	intron/exon	EPI-2195-12	IL-2 R
15 CTG TGC BCC TCT C	<u>3081</u> [3080]	3'UTR	EPI-2203-05	IL-6 R HSIL6R
CBG TGC BCC BCT CBC CTG	<u>3082</u> [3081]	intr/ex	EPI-2203-06A	HSIL2rG6
G TGC BCC BCT CBC CTG	<u>3083</u> [3082]	intr/ex	EPI-2203-06B	HSIL2rG6
CBC CTC TCB CCT GGG	<u>3084</u> [3083]	coding	EPI-2203-07A	HUMIL71
C CTC TCB CCT GGG	<u>3085</u> [3084]	coding	EPI-2203-07B	IL-7 HUMIL71
GCT CCB CTC GCC T	<u>3086</u> [3085]	coding	EPI-2203-08	IL-6 R HSI6REC
20 TGC TCC TCB CGC C	<u>3087</u> [3086]	intron PDGF A	EPI-2303-09	Chain HUMPDGFAB
GTT GTT GBT CTG G	<u>3088</u> [3087]	3'utr	EPI-2199-01	GATA-4Transcrip. Factor for IL-5
GGT TGB BBT TGG TCT TGG	<u>3089</u> [3088]	Coding	EPI-2199-02	TNF α HUMTNFA
GGT TGT TGB TGB TCT G	<u>3090</u> [3089]	Far 5'UTR	EPI-2199-03	HSSUBP1G(Sub Pr)
25 GGG TTB BBG TTG BTC TGG	<u>3091</u> [3090]	Coding	EPI-2199-04	NeutrophilAdh. R HUMNARIA
GGG TTB BBG TTG BTC TGG	<u>3092</u> [3091]	HSHM2	EPI-2199-05	m2 Muscarinic R
TTG TTG TBG BTC TGG	<u>3093</u> [3092]	HUML1CAM	EPI-2199-06	L1 LeukAadhProt
GGG TBG BBG BGT CCG CTG	<u>3094</u> [3093]	coding	EPI-2203-01	HUMGATA2A
30 GGG TCB GBG GBT CBG CTG	<u>3095</u> [3094]	S71424S2	EPI-2203-02	IGE eps
GGG TBG GTG GGT C	<u>3096</u> [3095]	coding	EPI-2203-03	HSGCSFR2
GGG TCG GBG GGT CBG C	<u>3097</u> [3096]	HUMITGF	EPI-2203-04	TGF β 3
GGG TGG GCT T	<u>3098</u> [3097]	HUMNK65PRO	EPI-2206-01	NFKB/NK & TCell
35 GGG TGG GCT TGG G	<u>3099</u> [3098]	HUMPEREEB	EPI 2206-02	Activating Prot NFKB/Prostagl. EP3 Rec
CCTGGGTGGGBBTGGG	<u>3100</u> [3099]		EPI 2206-03	HSNF2B/GCSF NFKB/GranuLocCSF/Transcr. FactorNF2B
40 CCTGGBTGGGCBTGGG	<u>3101</u> [3100]		EPI-2206-04	HUMLAP/NFKB Leuk. Adhes. Prot
GCCTGBGTGBBCTTGGG	<u>3102</u> [3101]		EPI2206-05	NFKB/Endothel N2 S63833
45 CCCAVGVCCVCCAGGC	<u>3103</u> [3102]		EPI 2206-06	NFKBAS13/B Lymph SerThrProt. Kinase
AGCCCACCCAGGC	<u>3104</u> [3103]		EPI2206-07	NFKBAS13/GCSF1 HSGCSFR1Rec
50 BCCTGGGTGGGCTB	<u>3105</u> [3104]		EPI2206-08	NFKBAS13/GCSF1/ NK7TCELLACT. Prot
GGTGGGCTTGGG	<u>3106</u> [3105]		EPI 2206-09	NFKBAS13/ HSTGFB1 TGFB
CCBBGGTGGGCTTGGG	<u>3107</u> [3106]		EPI 2206-10	NFKBAS13/ HSTGFB1 TGFB1
55 CTGGGTGGGBBTGGG	<u>3108</u> [3107]		EPI 2206-11	NFKBAS13/ HSGCSFR1 GCSFR1
CCBGGGTGGGCTTGG	<u>3109</u> [3108]		EPI 2206-12	NFKBAS13/HUMCD30A LymphActAntigCoding
GGGTGGGCTTGG	<u>3110</u> [3109]		EPI-2206-12B	NFKBAS13/HUMCD30A
60 CCTGBGTGBGCBTGGG	<u>3111</u> [3110]		EPI 2206-13	NFKBAS13/HUMCAM1V Vasc. Endoth. Cell Adh. Molec

B: Universal Base

The MTA oligos of Table 3 are suitable for use with two or more of the targets listed in Table 4 below.

CLEAN VERSION



In the specification

Please enter the following pages 296 through 298 for the substitution of the previous original pages (starting from next page):